YALE JOURNAL OF BIOLOGY AND MEDICINE 67 (1994), pp. 173-180.

Dragstedt, Gastric Acid and Duodenal Ulcer

Michael Hobsley[a]

University College London Medical School, London, United Kingdom

(Received February 25, 1994; returned for revision May 2, 1994; accepted August 23, 1994)

Dragstedt believed that basal hypersecretion of gastric acid was the root cause of duodenal ulcer, that the hypersecretion was due to an increased vagal stimulation, and that vagotomy would therefore cure duodenal ulcer. He introduced vagotomy and demonstrated that the operation was successful in curing most patients of their duodenal ulcers. This article reviews how further research in the succeeding half century has demonstrated that it is the effect of vagotomy on stimulated, rather than upon basal secretion that cures duodenal ulcer and that the apparent basal hypersecretion of patients with duodenal ulcer is due to an increased parietal cell mass. The article points out that there is no convincing explanation as yet of the mechanism whereby vagotomy reduces histamine-stimulated gastric secretion.

INTRODUCTION

Dragstedt's massive contribution as scientist and surgeon was to introduce vagal section as a treatment for chronic duodenal ulcer. His rationale was pithily summarized by him in 1956 [1]: "I believe that duodenal ulcers are due to a hypersecretion of gastric juice in the empty stomach dependent upon excessive and abnormal secretory impulses in the vagus nerves." He emphasized in his first [2] and subsequent publications [3-5] that nocturnal (i.e., basal) secretion was greatly reduced by operation, usually to a level less than that seen in normal controls.

The purpose of this review, 50 years after his seminal paper, is to examine Dragstedt's hypothesis in the light of subsequent advances in knowledge. The links in the chain that require examination are:

1. Is duodenal ulcer associated with increased gastric acid secretion?
2. Does vagotomy reduce gastric acid secretion? And is any such reduction related to freedom from recurrence of the disease?
3. If the above are confirmed, is resting juice the element of gastric secretion that it is critical to reduce, or is it some other aspect that is fundamental?
4. How does vagotomy reduce gastric secretion?

IS DUODENAL ULCER ASSOCIATED WITH INCREASED GASTRIC ACID SECRETION?

There is no reasonable doubt that this association exists in terms of maximally (histamine or pentagastrin) stimulated secretion [6]. Maximal gastric secretion, i.e., the output rate of acid that can be achieved using maximal concentrations of a powerful secretagogue

[a]*To whom all correspondence should be addressed:* M. Hobsley, Department of Surgery, UCLMS, 67-73 Riding House Street, London W1P 7LD, United Kingdom. Tel: (44) 171-380-9312; Fax: (44) 171-636-5176; E-mail: m.hobsley@ucl.ac.uk.

[b]*Abbreviations:* ECL, the enterochromaffin-like cell; Kx, the dose of an agonist that would produce half the theoretical maximal response, calculated from the dose-response curve after transformation to a straight line; VG, the volume of gastric secretion collected in a stated time interval from the stomach by nasogastric aspiration, corrected for pyloric losses, sequestration within the stomach, and duodenogastric reflux; VGmax, the theoretical maximal secretory response of the stomach, corrected as above and derived by calculation from the linear transformation of the dose-response curve.

such as histamine or pentagastrin, is an important concept in gastric physiology because there is evidence that it represents the stimulated output of the whole of the parietal cell population [7, 8], the parietal cell mass as it is usually called. However, there is considerable overlap between the ranges of maximal gastric secretion of normal subjects and duodenal ulcer patients [9] so that the maximal secretion of about three-quarters of duodenal ulcer subjects lies within the range of normal and only one-quarter of normals have a gastric secretion so low as to lie below the lower boundary of the duodenal ulcer group. Maximal gastric secretion depends on lean body mass [10] and other attributes of stature together with age [11], but these factors are not sufficient to explain the overlap. Nevertheless, the measurement of maximal secretion in any individual enables one to assess the chance that he comes from the duodenal ulcer rather than the control group, and that chance increases regularly with increasing secretion [12].

Have we a candidate to postulate as a likely cause for the increased maximal secretion? The answer is yes, but it is necessary to diverge from the main argument to consider the history of the relationship between cigarette smoking and duodenal ulcer.

Cigarette smoking and prevalence of duodenal ulcer

In 1927, Barnett was the first person to notice that duodenal ulcer seemed to be more common in habitual smokers than in non-smokers, although he did not believe that the association was meaningful [13]. Later observers were more impressed by the relationship, and in 1979 Harrison [14] reviewed six major studies and found that the mean prevalence ratio of duodenal ulcer in smokers compared with nonsmokers was 1.9:1. A subsequent epidemiological survey showed that in men, 75 percent of the attributable risk of duodenal ulcer could be abolished by removing (statistically) exposure to smoking and alcohol, alone or in combination [15]. This is of an order similar to that observed between cigarette smoking and lung cancer. More recently, an endoscopic survey of 1200 outpatients found a prevalence ratio of 7.8:1 [16].

Smoking and treatment of duodenal ulcer

There is also evidence that smoking has a deleterious effect on the healing rate of duodenal ulcer in response to H_2 antagonists and on the duration of the symptom-free period after the healing of a duodenal ulcer [17].

Smoking and gastric acid secretion

Does the effect of smoking on the incidence, rate of healing and relapse rate of duodenal ulcer act through an increase of parietal cell mass? The published evidence is substantially in favor of an association between cigarette smoking and maximal gastric secretion [18-22].

The last two quoted papers demonstrated that in patients with duodenal ulcer who smoke, there is a highly significant direct correlation between maximal gastric secretion and the total number of cigarettes that the individual has smoked. Standardization of maximal gastric secretion to zero smoking, i.e., mathematically expunging the putative effect of smoking on maximal gastric secretion, reduces the maximal secretion of these duodenal ulcer smokers towards, if not completely to, the range of normal non-smokers.

If this positive relationship between smoking and maximal gastric secretion is causative, we do not know the precise mechanism, but there is some suggestion that chronic smoking acts through the effect of acute smoking [23]. When the subject smokes a cigarette, after a plateau of sub-maximally stimulated gastric secretion has been reached during a continuous intravenous infusion of histamine, the gastric secretion is reduced below the plateau value. The repetition of this phenomenon several times

each day must lower the average acidity of the gastric contents, and we know that a tendency towards alkalinity in the neighborhood of the pyloric antrum increases the gastrin drive. Gastrin is not only a secretagogue: it also stimulates hyperplasia of parietal cells. And it is the total number of parietal cells, the parietal cell mass, that determines maximal gastric secretion. Whatever the mechanism, the evidence is solid that the risk of developing a duodenal ulcer is positively related to the number of parietal cells present in the subject's stomach; and also to smoking , as discussed above.

The advent of *Helicobacter pylori* has not destroyed the relationship between duodenal ulcer, maximal gastric secretion and smoking. The precise role of the organism in the etiology of duodenal ulcer remains undecided. In some series, over 90 percent of patients with duodenal ulcer have the organism in their gastric mucus, and there are many reports that eradicating the organism with antibiotics, especially in combination with protein pump inhibitors, provides longer periods of healing even amounting to "cure." On the other hand, in some countries the organism is highly prevalent despite the fact that duodenal ulcers are rare. Clearly, much further work needs to be done, but from the viewpoint of this review the important consideration is that *H. pylori*, if it produces duodenal ulcer, does not do so by increasing maximal gastric secretion. The latest evidence seems quite clear that it reduces maximal gastric secretion [24].

DOES VAGOTOMY REDUCE GASTRIC ACID SECRETION?

Most authors who have studied basal secretion before and after vagotomy agreed that the operation reduces basal secretion, by anything between 50-90 percent [25-27], but the small volumes of gastric juice obtained from the unstimulated stomach and the apparent variability of basal secretion between 10- or 15-min collection periods resulted in a considerable overlap between the pre- and post-operative groups [28-30]. It was therefore difficult to deduce from changes in basal secretion whether an adequate vagotomy has been performed. Indeed, it now seems likely that the observations of these authorities were in error because they did not take into account the collection errors that beset aspirated gastric juice samples, especially when the secretion rate is low. After all possible collection errors (pyloric loss, sequestration within the stomach, duodenogastric reflux) [31-33] are corrected, one cannot demonstrate a reduction in basal secretion after vagotomy [34], although that study confirmed that patients with duodenal ulcer as a group had a significantly greater basal secretion than normal subjects. On the basis of this evidence one must conclude that the case for basal hypersecretion being the cause for duodenal ulcer, and elimination of this basal hypersecretion by vagotomy being the explanation of the efficacy of the operation at healing duodenal ulcer is not proven.

Theoretically, the correct test for the effect of the presence or absence of vagal innervation on gastric secretion should be something like the insulin-hypoglycemia test of Hollander [35]: in the presence of the vagus, hypoglycemia stimulates the vagal center to drive secretion. A huge literature grew up about the post-vagotomy insulin test, in particular attempting to define its use to indicate a "complete" vagotomy. The Hollander criteria [36, 37] were the first and the most popular but were unreliable because they depended upon the titratable acidity of the gastric juice, that is the variable whose measurement is the most likely to be inaccurate because of alkaline duodenogastric reflux [38]. If secretion in response to insulin were corrected for reflux, and also for pyloric losses and sequestration (the index known as VG^b) and standardized for stature, the level to which it fell after vagotomy provided a better prognostic index for the risk of recurrence [39].

The hypoglycemia produced by insulin is unpleasant and could be dangerous, and vagal stimulation by sham feeding produced a smaller response with the vagus intact than did insulin and therefore provided a less sensitive index. Histamine-stimulated secretion

is also reduced by vagotomy [14 and numerous other papers], and again it was found that the level to which histamine-stimulated secretion fell after vagotomy provided an accurate prognostic index of the likelihood of a long-lasting cure [40].

WHAT ELEMENT OF GASTRIC SECRETION IS IT CRITICAL TO REDUCE?

Some comments above have indicated that the essence of the prognosis about whether the duodenal ulcer is likely to have been cured by the vagotomy is given by the level to which histamine- or insulin-stimulated secretion falls. Furthermore, it cannot be convincingly demonstrated that vagotomy reduces basal secretion [34] The same paper, however, confirmed that basal secretion is indeed larger in duodenal ulcer patients than in normal controls.

These three statements do not fit very comfortably together. Dragstedt interpreted the increased basal secretion in duodenal ulcer patients compared with controls (the "increased vagal drive") as the cause of the duodenal ulcer disease. He knew that vagotomy would reduce stimulated gastric secretion and therefore reasoned that the operation should reduce basal gastric secretion and thereby cure the ulcer. This reasoning seemed to be supported by the excellent clinical results of vagotomy: the ulcers healed, and in most cases remained healed. While in the early days, the evidence suggested that the vagotomy reduced basal secretion, that seemed further support for his hypothesis. However, it now appears that basal secretion is not reduced by vagotomy, so it is difficult to accept that the increased vagal drive caused the ulcer. And yet the vagotomy does heal the ulcer and is associated with a reduction in stimulated gastric secretion. What is the cause of the basal hypersecretion if it does not respond to vagotomy, and why is it present in patients with duodenal ulcer if it is not the cause of the ulcer?

A recent study [41] has answered these questions. Dose-response curves were constructed for increasing doses (including zero, i.e., basal secretion) of histamine in patients with duodenal ulcer and control subjects, including both smokers and non-smokers. These curves were analyzed mathematically by the Hofstee transformation, which converts the parabola of the dose-response curve into a straight line rather than the more familiar Lineweaver-Burke plot because the Hofstee has been found to be more reliable in the circumstances of this study [42 and Figure 1]. The parameters obtained by this technique are VGmax, the theoretical maximal secretion that would be obtained with an infinite dose of histamine, and Kx, the dose producing half the theoretical maximal response. Not surprisingly, duodenal ulcer patients had a greater maximal secretion than controls, but the half-response doses were identical. Moreover, basal secretion as a fraction of the theoretical maximum was identical in the two groups. Smokers did not differ from non-smokers in respect of these parameters.

We may now try to put together all the findings of this sensitivity study. The increased basal secretion of patients with duodenal ulcer turns out to be a scale-phenomenon: the larger parietal cell mass, as measured with maximal histamine, produces a larger acid output response to whatever is the stimulus that evokes resting gastric secretion. The two other possible explanations that were available before this study have been explicitly ruled out by the study. There is no increased sensitivity of the parietal cells to a normal, basal drive because the fraction (basal secretion/maximal secretion) in duodenal ulcer patients is identical with that in normal controls. Similarly, there is no increased basal drive acting upon cells of normal sensitivity. The conclusion has to be that the greater resting secretion in patients with duodenal ulcer is due to a normal basal drive acting upon a larger number of normally-sensitive parietal cells. Smoking alters neither basal drive nor parietal cell sensitivity but, as discussed previously, increases maximal gastric secretion by increasing the number of parietal cells

HOW DOES VAGOTOMY REDUCE GASTRIC SECRETION?

We now know so much about the receptors, messengers and the hydrogen ion pump of the parietal cell and its relations with the ECL cell, that this question may seem superfluous. Yet in many ways this abundance of knowledge is illusory. We know that vagotomy reduces maximal gastric secretion as evoked by a "maximal" dose of histamine, but we do not know how this effect is achieved. The problem is that there are two viewpoints of the relationship between vagally stimulated and maximally (histamine) stimulated gastric secretion that remain difficult to reconcile. One claims that the vagus in some way heightens the sensitivity of the parietal cell to histamine so that, provided the vagal innervation of the stomach is intact, the histamine produces maximal secretion. According to this view, vagotomy results in a submaximal response of the parietal cells to histamine because of the lack of this background of sensitization. On the other hand, many secretion data point to the firing of a parietal cell being an all-or-none response [7, 8].

The facts of the relationship between insulin- and histamine-stimulated secretion in patients before and after vagotomy are that (maximally) histamine-stimulated secretion

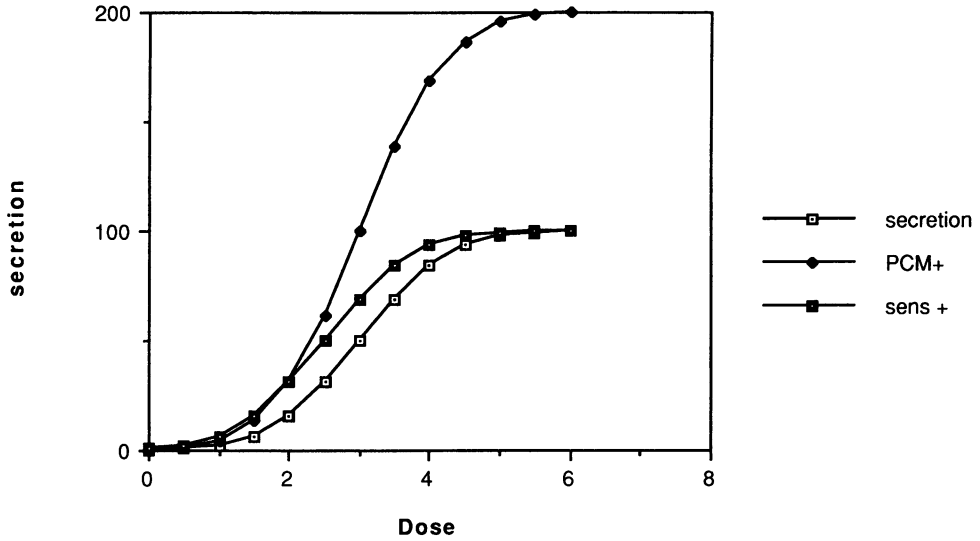

Figure 1. Hypothetical dose response curves for the output-rate of gastric acid secretion in response to an agonist. Both dose and response are in arbitrary units. The curve marked "secretion" represents a normal subject, that marked sens+, a subject with increased sensitivity, and that marked PCM+, a subject with an increased parietal cell mass. All three curves rise to a plateau at maximal dose, but the plateau reached by the PCM+ curve is higher than that of the other two curves because it represents the output of a larger number of fully-stimulated parietal cells. At a dose of two units, which one may represent as basal secretion, the secretion of both the abnormal subjects is equal, and greater than that of the normal subject. However, the fraction (basal/maximal) is greater for the sens+ curve than for the PCM+ curve, the latter fraction having the same value as on the normal curve. The same basal secretion on the normal curve might have represented an increased basal drive, but in that case the fraction (basal/maximal) secretion would also have been greater than normal.The evidence suggests that duodenal ulcer subjects owe their apparently greater basal secretion neither to increased basal drive nor to increased parietal cell sensitivity, but to an increased parietal cell mass.

exceeds vagally stimulated secretion by a constant amount per unit time, and that there is no significant difference in this excess whether the vagus is normal or the patient has had a complete vagotomy or an incomplete vagotomy [40]. This constant excess militates against a sensitization phenomenon, which might be expected to follow a dose-related pattern in which case the excess after a partial vagotomy would be less than after complete vagotomy. Instead it favors the suggestion made in that paper that there are two types of parietal cells: one responds to either histamine or the vagus, but only if the vagal innervation of the cell is intact; the other responds only to histamine but not to the vagus, and the histamine-response does not require the vagal innervation to be intact. As far as the writer knows, this suggestion has not been further explored. In the light of present knowledge, the link might be provided by the ECL cell which we know to be the source of histamine secretion. Maybe parietal cells, which have an ECL cell close by, have no need to depend upon the vagus while those without such a neighbor require the vagal stimulation before they will respond to histamine secreted by distant ECL cells.

CONCLUSION

No scientist ever explains "truth" so completely that the subject yields no new information to subsequent workers. We need not be surprised, therefore, that Dragstedt's hypothesis of an increased vagal drive and the consequent basal hypersecretion of acid as the cause of duodenal ulcer has not been supported by later work. Nevertheless, his operation of vagotomy worked: it reduced stimulated gastric secretion and the ulcers healed.

To a considerable extent, they stayed healed although, as with all treatments, there were sometimes unwanted side-effects. Until the advent of the H_2-antagonists, vagotomy remained the most effective and reliable treatment for the condition, and with fewest side-effects. At the same time, the vagotomy effect on gastric secretion led to an intense study of gastric secretory physiology, which has yielded much new scientific information and still continues to be a productive vein. We indeed salute the memory of a great scientist and a great surgeon.

REFERENCES

1. Dragstedt, L.R. Excerpta Medical Section IX: Surgery Vol. 10, 1956, quoted by Garnott Allen, J.G., In The Physiology and Treatment of Peptic Ulcer. Chicago: University of Chicago Press; 1959, pp. 231.
2. Dragstedt, L.R. and Owens, F.M., Jr. Supradiaphragmatic section of vagus nerves in the treatment of duodenal ulcer. Proc. Soc. Exp. Biol. Med. 53:152-154, 1943.
3. Dragstedt, L.R., Palmer, W.L., Schafer, P.W., and Hodges, P.C. Supradiaphragmatic section of the vagus nerves in the treatment of duodenal and gastric ulcers. Gastroenterology 3:450-462, 1944.
4. Dragstedt, L.R. Section of vagus nerves to the stomach in the treatment of peptic ulcer. Surgery 21:144, 1947.
5. Woodward, E.R., Harper, P.V., Tovee, E.B., and Dragstedt, L.R. Effect of vagotomy on gastric secretion in man and experimental animals. Am. Med. Assn. Arch. Surg. 59:1191-1212, 1949.
6. Polland, W.S. Histamine test meals. Arch. Int. Med. 51:903-919, 1933.
7. Card, W.I. and Marks, I.N. The relationship between the acid output of the stomach following maximal histamine stimulation and the parietal cell mass. Clin. Sci. 19:147-163, 1960.
8. Cheng, F.C.Y., Lam, S.K., Ong, G.B. Maximum acid output to graded doses of pentagastrin and its relation to parietal cell mass in Chinese patients with duodenal ulcer. Gut 18:827-832, 1977.
9. Kay, A.W. An augmented histamine test. Brit. Med. J. 2:77-80, 1953.
10. Baron, J.H. Lean body mass, gastric acid and peptic ulcer. Gut 10:637-642, 1969
11. Hassan, M.A. and Hobsley, M. The accurate assessment of maximal gastric secretion in control subjects and patients with duodenal ulcer. Brit. J. Surg. 58:171-179, 1971.
12. Hobsley, M., Whitfield, P.F. The likelihood of disease in relation to the magnitude of a risk factor: the example of duodenal ulcer. Theor. Surg. 2:106-109, 1987.

13. Barnett, C.W. Tobacco smoking as a factor in the production of peptic ulcer and gastric neurosis. Boston Med. Surg. J. 197:457-459, 1927.
14. Harrison, A., Elashoff, J., and Grossman, M.I. Cigarette smoking and ulcer disease. The Surgeon-General's report on smoking and health. Section 9, 5-21. U.S. Department of Health, Education and Welfare, Public Health Service, 1979.
15. Piper, D.W., Nasiry, R., McIntosh, J., Shy, C.M., Pierce, J., and Byth, K. Smoking, alcohol,analgesics and duodenal ulcer. Scand. J. Gastroenterol. 19:1015-1021, 1984.
16. Ainley, C.C., Forjacs, I.C., Keeling, P.W.N., and Thompson, R.P.H. Outpatient endoscopic survey of smoking and peptic ulcer. Gut 27:648-651, 1986.
17. Korman, M.G., Hansky, J., Eaves, E.R., and Schmidt, G.T. Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. Gastroenterology 85:871-874, 1983.
18. Whitfield, P.F. and Hobsley, M. Smoking and gastric hypersecretion in duodenal ulcer patients. Gut 20:A918, 1979.
19. Parente, F., Lazzaroni, M., Sangaletti, O., Baroni, S., and Porro, G.B. Cigarette smoking, gastric acid secretion, and serum pepsinogen I concentrations in duodenal ulcer patients. Gut 26:1327-1332, 1985.
20. Massarratt, S., Enschai, F., and Pittner, P.M. Increasing gastric secretory capacity in smokers without gastrointestinal lesions. Gut 27:433-439, 1986.
21. Whitfield, P.F. and Hobsley, M. Maximal gastric secretion in smokers and non-smokers with-duodenal ulcer. Brit. J. Surg. 72:955-957, 1985.
22. Whitfield, P.F. and Hobsley, M. Comparison of maximal gastric secretion in smokers and non-smokers with and without duodenal ulcer. Gut 28:557-560, 1987.
23. Roxburgh, J.C., Whitfield, P.F., and Hobsley, M. Effect of acute cigarette smoking on gastric secretion. Gut 33:1170, 1992.
24. Chandrakumaran, K., Vaira, D., and Hobsley, M. Duodenal ulcer, *Helicobacter pylori* and gastric secretion. Gut, in press, 1994.
25. Farmer, D.A., Howe, C.W., Porell, W.J., and Smithwick, R.H. The effect of various surgical procedures upon the acidity of the gastric contents of ulcer patients. Ann. Surg. 144:319-331, 1951.
26. Amdrup, E. and Jensen, H-E. Selective vagotomy of the parietal cell mass preserving innervation of the undrained antrum. Gastroenterology 59:522-527, 1970.
27. Johnston, D., Wilkinson, A.R., Humphrey, C.S., Smith, R.B., Goligher, J.C., Kragelund, E., and Amdrup, E. Serial studies of gastric secretion in patients after highly selective (parietal cell) vagotomy without a drainage procedure for duodenal ulcer. I. Effect of highly selective vagotomy on basal and pentagastrin-stimulated maximal acid Output. Gastroenterology 64:1-11, 1973.
28. Ross, B. and Kay, A.W. The insulin test after vagotomy. Gastroenterology 46:379-386, 1964.
29. Kronborg, O. Pre-and post-operative insulin tests in patients with duodenal ulcer: comparison with the augmented histamine test. Scand. J. Gastroenterol. 5:687-693, 1970.
30. Cowley, D.J., Spencer, J., and Baron, J.H. Acid secretion in relation to recurrence of duodenal ulcer after vagotomy and drainage. Brit. J. Surg. 60:517-522, 1973.
31. Hobsley, M. and Silen, W. Use of an inert marker (phenol red) to improve accuracy in gastric secretion studies. Gut 10:787-795, 1969.
32. Hobsley, M. Pyloric reflux: a modification of the two-component hypothesis of gastric secretion. Clin. Sci. Molec. Med. 47:131-141, 1974.
33. Fiddian-Green, R.G., Parkin, J.V., Faber, R.G., Russell, R.C.G., Whitfield, P.F., and Hobsley, M. The quantification in human gastric juice of duodenogastric reflux by sodium output and by bile-labelling using Indocyanine Green. Klin. Wochensch. 57:815-824, 1979.
34. Faber, R.G. and Hobsley, M. Basal gastric secretion: reproducibility and relationships with duodenal ulcers. Gut 18:57-63, 1977.
35. Hollander, F., Jemerin, E.E., and Weinstein, V.A. An insulin test for differentiating vagal from non-vagal stomach pouches. Federation Proc. 1:116, 1942.
36. Hollander, F. The insulin test for the presence of intact nerve fibres after vagal operations for peptic ulcer. Gastroenterology 7:607-614, 1946.
37. Hollander, F. Laboratory procedures in the study of vagotomy (with particular reference to the insulin test). Gastroenterology 11:419-425, 1948.
38. Faber, R.G., Russell, R.C.G., Royston, C.M.S., Whitfield, P.F., and Hobsley, M. Duodenal reflux during insulin-stimulated secretion. Gut 15:880-884, 1974.
39. Maybury, N.K., Faber, R.G., and Hobsley, M. Post-vagotomy insulin test: improved predictability of ulcer recurrence after corrections for height and collection errors. Gut 18:449-456, 1977.

40. Boulos, P.B., Faber, R.G., Whitfield, P.F., Parkin, J.V., and Hobsley, M. Relationship between insulin- and histamine-stimulated secretion before and after vagotomy. Gut 24:549-556, 1981.
41. Roxburgh, J.C., Whitfield, P., and Hobsley, M. Parietal cell sensitivity in man: control and duodenal ulcer subjects, smokers and nonsmokers. Europ. J. Gastroenterol. Hepatol. 6:235-240,1994.
42. Dowd, J.E. and Riggs, D.S. A comparison of estimates of Michaelis-Menten kinetic constants from various linear transformations. J. Biol. Chem. 240:863-869, 1965.